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Intracranial synovial sarcoma: A clinical, radiological and pathological study of 16 cases☆

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ABSTRACT

Introduction: Synovial sarcoma (SS) is a tumor of unknown origin and is extremely rare in the central nervous system. Most studies on intracranial SS included only one or two cases. To better understand the disease, we review a series of primary intracranial SS.

Method and materials: 16 primary intracranial SS in Tiantan Hospital during 2008–2017 were included. The clinical characteristics, including radiological and histological examination, operative records, and prognoses were reviewed.

Result: The case series included nine male and seven female patients with an average age of 23.8 years. Radiological results showed that the supratentorial region (81.25%) was the most common site of the brain involved. All patients were misdiagnosed as non-SS tumors. Gross total resection (GTR) was achieved in 12 cases (75.0%), and subtotal resection (STR) was achieved in 4 cases. All cases showed the characteristic SYT-SSX fusion gene, as detected by RT-PCR. The mean progression-free survival time (PFS) was 10.0 months and the mean overall survival time (OS) was 15.5 months. Multivariate analysis revealed that GTR and postoperative adjuvant radiotherapy were independent factors for PFS (HR = 6.143, 95% CI = 1.491–25.312; $P = 0.012$, HR = 6.143, 95% CI = 1.491–25.312; $P = 0.012$ respectively) and OS (HR = 9.000, 95% CI = 1.627–49.773; $P = 0.012$, HR = 0.017, 95% CI = 0.001–0.213; $P = 0.002$ respectively).

Conclusion: Intracranial SS were more frequently observed in the supratentorial region and in young patients without sex predilection. We recommend adjuvant radiation regardless of the extent of resection. More patients and longer follow-up periods were needed to further elucidate the biological features of intracranial SS.

1. Introduction

Synovial sarcoma (SS) is an aggressive soft tissue sarcoma with unknown histological origin. It usually occurs in the extremities of younger adults. However, any site in the body can be involved with SS. Cases of SS at unusual sites — including the tongue, esophagus, larynx, pleuropulmonary, mitral valve, thyroid gland, kidney, vulva, abdominal wall, prostate and peripheral nerves — have been reported in several literatures [1–11]. It has been well reported in recent years that SS could metastasize to central nervous system (CNS) [12–14],however, reports of intracranial synovial sarcoma are still rare [15–22]. (Table 1). It is quite a pity that these studies reported too few cases to show general characteristics of intracranial SS. Here, we searched the cases by pathological diagnosis of SS

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Table 1
The clinicopathological characteristics of primary intracranial synovial sarcoma found in the literature.

Literature	Year	Gender/Age	Symptoms at presentation	Intracranial findings	Outcome
Kleinschmidt-DeMasters et al. [15]	1998	F/19	Fatigue, nausea, Bell's palsy, amenorrhea, headache, polydypsia, severe hirsutism	Third ventricle mass	Died six months later
Scheithauer et al. [16]	2007	M/48	Right-sided headache and blurred vision	Right sellar and parasellar mass	Survival at least eleven months
Horbinski et al. [17]	2008	M/81	Right-sided weakness, difficulty with ambulation and speech	Left parietal lobe mass	Survival at least five months
Katsaros et al. [18]	2008	F/15	Gradual pain of the dorsal neck	The mass extends from the right petrous bone to the occipital bone at the level of the foramen magnum	Died fourteen months later
Lin et al. [19]	2013	M/21	Mild headache and general vertigo	Right anterior cranial fossa mass	Survival at least six months
Xiao et al. [20]	2014	M/1	Crying and increasing unsteadiness of gait	Cerebellum mass	Survival at least six months
Patel et al. [21]	2016	M/21	Headache, ataxia, left hemianopsia, left arm weakness	Right parietal mass with hemorrhage	Survival at least 2 years
Sharma et al. [22]	2017	F/50	Left-sided hemiplegia	Right parafalcine mass	Unknown

through the chart review from the medical records database in our hospital, which included all the patients who discharged from hospital since 1980. We report a series of 16 patients with histologically confirmed intracranial SS and their long-term outcomes in a single center. To the best of our knowledge, this study is the largest case series of intracranial SS. We believe that the clinical, radiological and pathological features of intracranial SS we show here will provide valuable information for better diagnosis and treatment in the future.

2. Materials and methods

This retrospective study included 16 cases of intracranial SS, all of them were surgically treated and pathologically confirmed at Beijing Tiantan Hospital between January 2008 and January 2017 (Table 2). The relevant clinical data (including presentation, radiological imaging, pathology, treatment, and follow-up outcomes) were collected through a chart review and telephone interviews with an approval of the institutional review board.

Radiographic studies were reviewed extensively by two independent neuro-radiologists. The diagnosis of SS was pathologically confirmed by the Department of Neuropathology at Beijing Neurosurgical Institute using the 2013 World Health Organization Classification of Tumors of Soft tissue and Bone [23]. The estimation of the extent of tumor removal was acquired from the operation records or postoperative magnetic resonance imaging (MRI). Gross total resection (GTR) and subtotal resection (STR) were defined as total and subtotal macroscopic removal, respectively.

Fresh paraffin-embedded tumor tissue was cut into 5-μm slices and stained with hematoxylin and eosin (H&E). Immunohistochemical staining for Bcl-2, vimentin, SMA, EMA, CD99, CD34, S-100 was used for differential diagnosis of the samples. Cytogenetic analysis using fluorescence in situ hybridization (FISH) demonstrated SS18-SSX, an aberration specific for SS. Paired signals were defined as red and green signal less than 2 signal diameters apart or a single yellow (overlapping) signal, while unpaired signals were those separated by greater than or equal to 2 signal diameters from an oppositely colored signal. SS18-SSX translocation gene was defined as one paired signal and one unpaired signal in a nucleus. RT-PCR was used to detect the SYT-SSX fusion gene. Two independent neuropathologists reviewed the microscopic pathologies of the SS samples.

Since there was a possibility of intracranial metastasis of an SS arising in another anatomical location, the patients underwent a whole-body positron emission tomography/computed tomography (PET/CT) study to search for a potential primary tumor, but no abnormality was found.

Potential factors for PFS and OS were evaluated by Cox proportional hazard models. Independent prognostic factors with a $P < 0.1$ in the univariate analysis were further evaluated by the multivariate Cox proportional regression model.

3. Results

3.1. Patient demographics

The clinic characteristics and treatment of the 16 patients of intracranial SS were described in Table 2. The tumors occurred in 9 men and 7 women, ranging in age from 5 to 65 years (mean age, 23.8 years)1. The duration of symptoms ranged from 0.2 to 6.0 months with a mean length of 4.5 months. The preoperative symptoms included headache (n = 12, 75%), vertigo (n = 2, 12.5%), vomiting (n = 4, 25.0%), nausea (n = 2, 12.5%) and motor weakness (n = 3, 18.75%). None of the patients received previous radiotherapy or surgery.

3.2. Neuroimaging evaluation

The lesion locations mainly included the frontal lobe (n = 4, 25%), parietal lobe (n = 2, 12.5%), cerebellum (n = 2, 12.5%) and anterior skull base (n = 2, 12.5%), while temporal lobe, occipital lobe, lateral ventricle, third ventricle, sellar region and petroclival region were each observed in one case (6.25%). Seven lesions were located on the left side, six lesions were located on the right side, and three involved bilateral sides. Among the 16 lesions, 13 lesions (81.25%) were located in the supratentorial region, two (12.5%) was infratentorial seated and one (12.5%) was located both supra- and infra-tentorial region. Overt intralesional hemorrhage was observed in two patients (12.5%). Perilesional brain edema was detected in seven lesions (43.75%). The edema was moderate and estimated to be related to the intralesional hemorrhage in two of these lesions, whereas the other five lesions exhibited mild edema. Hydrocephalus was noted in two patients (12.5%), which was due to blockage of the bilateral Monro foramens by the lesions.

Based on the MRI, the tumor boundary was well-defined in 11 (68.75%) cases and poorly defined in five (31.25%). The morphology of the lesions was defined as cystic (n = 5, 31.25%) and solid (n = 11, 68.75%). The solid element of the tumor presented with hypointense T1 and hyperintense T2 signals in six cases (37.5%), mixed T1 and T2 signals in four cases (25%), and isointense T1 and T2

Table 2
Clinical, radiologic, and pathological characteristics of 16 intracranial synovial sarcoma.

No.	Sex/Age, years	Signs and symptoms	Location	Radiology	Treatment	Extent of resection	Immuno-histochemistry	Pathology type	Progression-free survival	Overall survival
1	F/15	headache, blurred vision and lethargy	left frontal lobe	cyst with surrounding edema	surgery + radiotherapy	GTR	positive: Bcl-2, MyoD1, S-100 SS18-SSX detected	monophasic	13 months	20 months
2	F/19	headache, fatigue, nausea, vomit	third ventricle	solid	surgery	STR	positive: EMA, CK, CD99 SS18-SSX detected	biphasic	5 months	6 months
3	M/36	headache and blurred vision	sellar region	solid	surgery + radiotherapy	GTR	positive: EMA, Bcl-2, CK SS18-SSX detected	biphasic	10 months	19 months
4	M/65	right-sided weakness, difficulty with ambulation and speech	left parietal lobe	solid with surrounding edema	surgery + radiotherapy	GTR	positive: P53, Bcl-2, vimentin, S-100 SS18-SSX detected	monophasic	9 months	14 months
5	F/18	gradual pain of the dorsal neck	right petroclival region	solid	surgery + radiotherapy	STR	positive: Bcl-2, vimentin, CK, CD99 SS18-SSX detected	biphasic	10 months	15 months
6	M/25	mild headache and general vertigo	right anterior cranial fossa	cyst with surrounding edema	surgery + radiotherapy	GTR	positive: CD99, Bcl-2, CK SS18-SSX detected	biphasic	11 months	17 months
7	M/5	crying and increasing unsteadiness of gait	right Cerebellum	solid	surgery	GTR	positive: CD99, Bcl-2, vimentin, SS18-SSX detected	monophasic	8 months	12 months
8	M/27	headache, ataxia, left hemianopsia, left arm weakness	right parietal lobe	solid with surrounding edema	surgery + radiotherapy + chemotherapy	STR	positive: Bcl-2, CK, CD99 SS18-SSX detected	biphasic	8 months	14 months
9	F/18	headache, blurred vision and lethargy	left temporal lobe	cyst with surrounding edema	surgery + radiotherapy	STR	positive: Bcl-2, SMA, Ki-67 SS18-SSX detected	monophasic	8 months	12 months
10	F/47	progressive headache and hyposmia	anterior skull base	solid	surgery + radiotherapy	GTR	positive: vimentin, CD99 SS18-SSX detected	biphasic	10 months	14 months
11	F/23	headache, vertigo, ataxia, vomit	left cerebellum	solid	surgery + radiotherapy	GTR	positive: vimentin, CD99, EMA, Bcl-2 SS18-SSX detected	biphasic	10 months	17 months
12	M/15	headache, memory deficit	left lateral ventricle	cystic	surgery + radiotherapy	GTR	positive: Bcl-2, EMA SS18-SSX detected	monophasic	14 months	19 months
13	M/14	headache, nausea, vomit	left occipital lobe	solid	surgery + radiotherapy + chemotherapy	GTR	positive: CD99, Bcl-2, S-100 SS18-SSX detected	monophasic	16 months	24 months
14	M/13	intermittent seizure	left frontal lobe	solid	surgery	GTR	positive: vimentin, Bcl-2, CK, CD99 SS18-SSX detected	biphasic	8 months	13 months
15	M/25	headache, vomit	right frontal lobe	cystic	surgery + radiotherapy	GTR	positive: vimentin, CK, Bcl-2, CD99 SS18-SSX detected	biphasic	11 months	21 months
16	F/16	headache, motor weakness	right frontal lobe	solid	surgery	GTR	positive: EMA, Bcl-2, S-100 SS18-SSX detected	monophasic	9 months	11 months

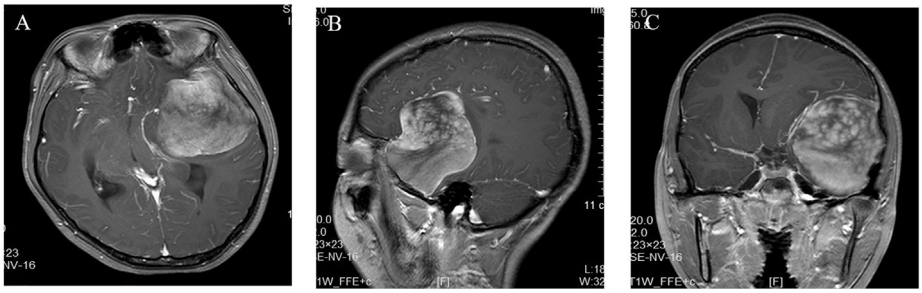

Fig. 1. Preoperative neuroimaging findings of the intracranial dura-based mass. (A) T1-weighted axial MRI demonstrated a large heterogeneous gadolinium-enhanced mass in the left middle cranial fossa. The mass was dura-based and the attached dura also showed heterogeneous enhancement. (B) On T1-weighted sagittal image, the solid mass showed heterogeneous enhancement and was observed to invade the left infratemporal fossa. (C) On T1-weighted coronal image, the mass compressed the left frontal and temporal lobes, and shifted the middle line to the opposite side.

signals in one case (6.25%). Of the 5 cases with cystic elements, the cystic component exhibited hypointense T1 and hyperintense T2 signals in 3 cases and mixed T1 and T2 signals in 2 cases. The tumor maximum diameter ranged from 1.6 to 5.6 cm with a mean size of 2.7 ± 1.3 cm.

According to MRI scans (Fig. 1), no patient was suspected preoperatively of having an intracranial synovial sarcoma, specifically, seven cases (43.75%) were diagnosed as astrocytoma, two cases (12.5%) each of ependymoma and subependymoma were diagnosed, and five cases each of (6.25%) ganglioglioneuroma, glioma, glioma with hemorrhage, pilocytic astrocytoma, and primitive neuroectodermal tumor (PNET) were diagnosed.

3.3. Surgical findings and outcomes

All tumors were removed through craniotomy under operative microscope. Intraoperatively, the lesions typically appeared grayish red, soft, crisp, hypervascularity, cystic mass containing xanthochromic fluid and partially attaching to the dura. Postoperative MRI indicated that GTR and STR were achieved in 12 patients (75.0%) and 4 patients (25.0%), respectively.

Postoperative complications occurred in four patients. Intracranial infection, partial seizure and new headache were each observed in one patient postoperatively and all of them were transient; the remaining patient (case 12) had pneumonia and lower cranial nerves (IX, X, XI and XII) deficits, and subsequently underwent tracheotomy. At discharge, five patients (31.25%) had improved, seven (43.75%) were unchanged, and four (25.0%) had worsened.

During follow-up, two patients received radiotherapy and chemotherapy with ifosfamide and doxorubicin after operation. Ten patients received postoperative radiotherapy. Four patients didn't receive any adjuvant therapy postoperatively. All patients suffered local recurrence, but no tumor metastasis during the follow-up, the mean progression-free survival time was 10.0 months. The mean overall survival time was 15.5 months. All patients died during the follow-up. Multivariate analysis revealed that GTR was an independent factor for PFS (HR = 6.143, 95% CI = 1.491–25.312; $P = 0.012$) and OS (HR = 9.000, 95% CI = 1.627–49.773; $P = 0.012$) and that postoperative adjuvant radiotherapy was an independent factor for PFS (HR = 0.081, 95% CI = 0.015–0.447; $P = 0.004$) and OS (HR = 0.017, 95% CI = 0.001–0.213; $P = 0.002$) (Table 3).

3.4. Pathological examination

Pathological analysis reported 9 (56.25%) biphasic subtypes and 7(43.75%) monophasic subtypes (Table 2). Biomarkers such as Bcl-2, CD99, CK, vimentin, EMA, S-100 and MyoD1 were always detected in 14, 10, 7, 7, 5 and 3 out of 16 SS respectively (Fig. 2). SS18-SSX was detected in all patients (Fig. 3).

4. Discussion

Synovial sarcoma is a kind of soft tissue sarcoma that occurs at any age and in any body region but tends to occur in middle-aged patients in the knee area, with a slight male predominance [24]. The neoplasm constitutes 5–10% of the soft tissue sarcomas [24]. Intracranial synovial sarcoma, especially primary intracranial SS is rare. The findings of the present series, the largest to date of genetically confirmed primary intracranial synovial sarcoma. Microscopically, synovial sarcomas showed the characteristic biphasic cellular pattern with epithelioid and fibrosarcoma-like areas in varying proportions [23]. A characteristic chromosomal translocation, t(X; 18) (p11.2; q11.2), has been identified on the molecular level [23,25]. Although “synovial” sarcoma tends to occur in periarticular areas, it is not actually associated with any synovial structure. Despite its name, it is no longer considered to be

Table 3
Univariate and multivariate analysis prognostic factors in the 16 intracranial synovial sarcoma.

Variable	Univariate analysis				Multivariate analysis			
	PFS		OS		PFS		OS	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value	HR(95%CI)	*P* value	HR(95%CI)	*P* value
Age > 18yrs	1.620 (0.526-4.985)	0.400	1.076 (0.384-3.016)	0.889				
Male	1.589 (0.547-4.617)	0.395	2.039 (0.706-5.890)	0.188				
Gross total resection	3.305 (0.943-11.586)	0.062	3.438 (0.916-12.903)	0.067	6.143 (1.491-25.312)	0.012	9.000 (1.627-49.773)	0.012
Postoperative adjuvant radiotherapy	0.149 (0.032-0.692)	0.015	0.043 (0.005-0.403)	0.006	0.081 (0.015-0.447)	0.004	0.017 (0.001-0.213)	0.002
Peritumor edema	1.297 (0.430-3.910)	0.645	1.241 (0.412-3.736)	0.701				
Solid or cystic tumor	1.829 (0.584-5.722)	0.300	1.706 (0.566-5.141)	0.343				
Pathology type	1.815 (0.550-5.992)	0.328	1.249 (0.436-3.580)	0.679				

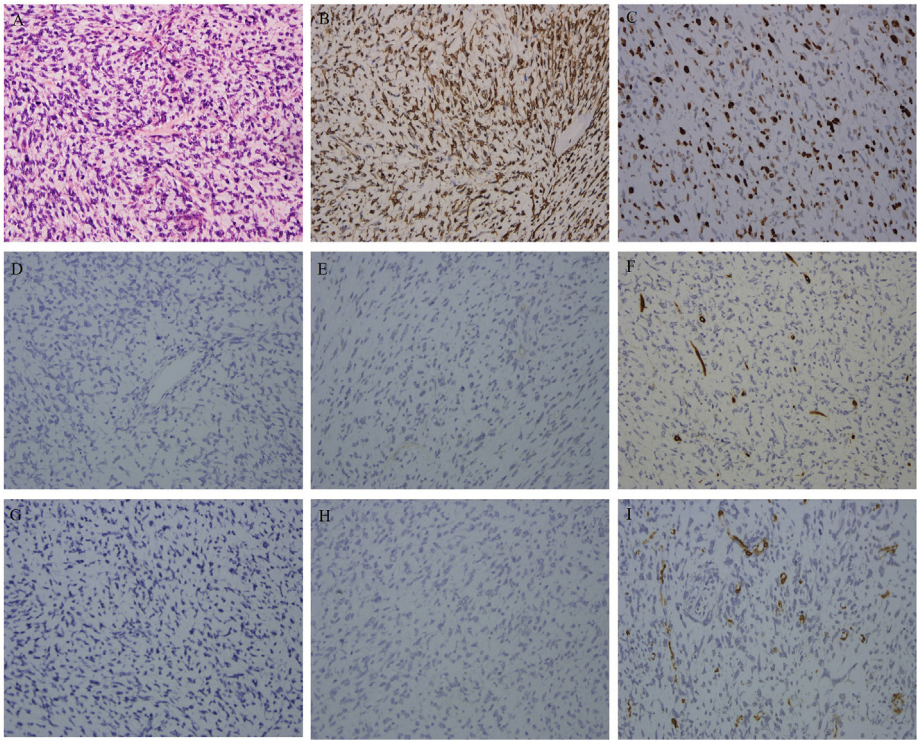

Fig. 2. Histomorphologic and immunohistochemical profile of dura-based synovial sarcoma. (A) High-power photomicrograph of the synovial sarcoma demonstrating short spindle tumor cells arranged in fascicles. The tumor cells depict moderate nuclear pleomorphism, inconspicuous nucleoli, and scant cytoplasm. (Hematoxylin and Eosin, original magnification × 200); (B) Tumor cells show diffuse and strong positivity for Bcl-2; (C) Tumor cells show a high Ki-67 index; (D) Tumor cells show negativity for GFAP; (E) Tumor cells show negativity for CD99; (F) Tumor cells show moderate positivity for CD34; (G) Tumor cells show negativity for Desmin; (H) Tumor cells show negativity for S100; (I) Tumor cells show moderate positivity for SMA (All the immunohistochemical staining are shown on original magnification × 200.).

histologically derived from the synovium but rather from a primitive mesenchymal cell.

The clinical symptoms and signs depend on the tumor site. They may include dysphagia, pain, hoarseness, headaches, and a palpable mass. The known sites of intracranial involvement are infratemporal fossa, paranasal sinuses, the orbit, sellar region, skull base and brain parenchyma. Przkora et al. also reported a case of synovial sarcoma presented with cerebral hemorrhage [26]. In our study, two cases of SS also presented with cerebral hemorrhage.

The preoperative diagnosis of intracranial SS is difficult. The preoperative misdiagnoses were mainly including atypical meningioma, hemangiopericytoma and glioma. The presence of calcification is typically associated with a better prognosis [27]. When bony involvement is suspected, a bone window CT should be ordered. An MRI is crucial to visualize the anatomic extent of the tumor. A chest x-ray is useful in looking for any pulmonary metastasis.

Synovial sarcoma may be confused with malignant meningioma because of their similar histological and immunohistochemical appearance (vimentin+, EMA+ and cytokeratin+). Most SS strongly co-express CD99 and bcl-2, and this pattern is highly distinct because it is generally not encountered in anaplastic meningiomas [28–30]. Other small round cell tumors arising in the brain also need differential diagnoses with SS, like mesenchymal chondrosarcoma, which is reported previously being lack of cytokeratin and EMA positivity, as well as SYT-SSX [31]. Though extremely scarce, synovial sarcoma also need differential diagnosis with malignant peripheral nerve sheath tumor (MPNST), which is seldom seen in cranium and mimic to SS in morphology. Recent studies suggest H3 trimethylation lost could be a helpful diagnostic clue to MPNST [32–34]. For synovial sarcoma, S-100 protein is focally expressed in nuclei or cytoplasm in approximately 40% of SS, including up to 40% of monophasic SS and 63% of poorly differentiated SS [35–37]. The t(X; 18) (p11.2; q11.2) chromosomal translocation is the cytogenetic hallmark of SS, of which the SS18 gene on 18q and either the SSX1 or SSX2 gene on Xp undergo a reciprocal translocation, forming a fusion SS18-SSX gene and subsequent fusion protein [24]. It has been revealed that more than 90% of SS present this characteristic molecular signature [38]. In our institution, SYT-SSX has been identified during the pathological diagnosis with suspicious SS since 2008. Such an analysis may be helpful when the diagnosis remains uncertain despite a thorough workup.

Since SS is extremely rare in the brain parenchyma, no optimal treatment has been systematically evaluated for intracranial SS so far. Compared with other variants of SS, poorly differentiated SS is aggressive, and metastasizes in a high percentage of cases. Claudia et al. reported that excellent local control and overall survival rates can be achieved with postoperative or definitive radiation therapy with acceptable acute and late toxicities in patients suffering from sarcomas of the head and neck region [39]. In our study, there was significant benefit between extent of tumor resection and prognosis. We recommend that the therapeutic regimen should include surgical resection of the tumor followed by adjuvant radiotherapy and chemotherapy, regardless of the extent of tumor resection. We do know that it can recur locally and that during the late stages of the disease, it has a predilection to metastasize to the lungs, pleura bone and lymph nodes. We recommend vigilant surveillance with clinical examinations and MRI scans during the follow-up period. However, the limitation in our cohort is the small sample size. We hope soon, there will be more SS cases reported in the whole world, which will help us to recommend a better treatment strategy.

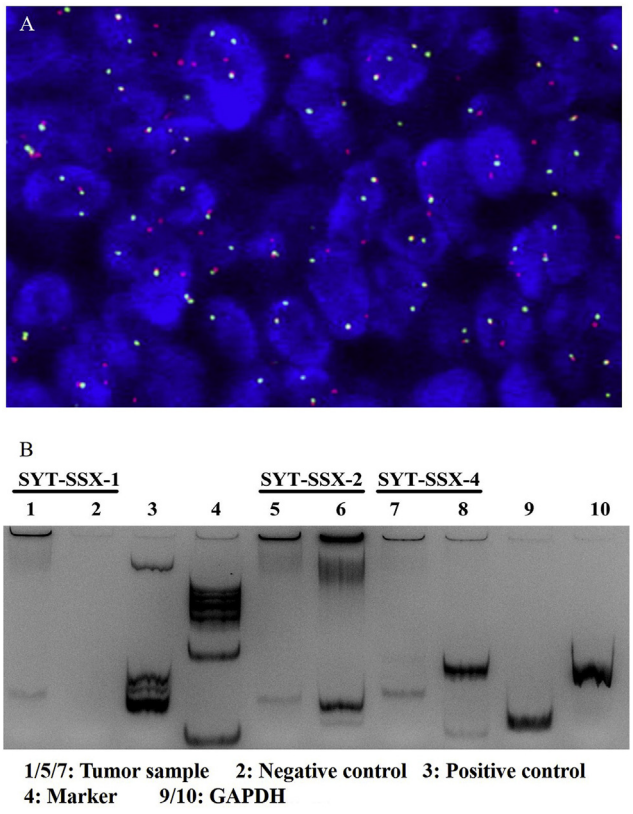

Fig. 3. Cytogenetic analysis of the dura-based synovial sarcoma. (A) Fluorescence in situ hybridization (FISH) with break-apart probe for SS18 gene, positive for t(X; 18) (original magnification × 400); (B) RT-PCR shows the tumor samples express the SYT-SSX fusion gene.

In summary, the current case series and literature review suggested that intracranial SS should be taken into consideration when intracranial lesions are detected in young patients. SS is a rare primary intracranial tumor and the diagnosis largely depends on histopathological examination. Neurosurgeons should be aware of this lesion entity. Unfortunately, intracranial SS usually has the poor prognosis, and GTR is expected whenever possible. After surgery, follow-up imaging examination is helpful for monitor.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of interest

No potential conflicts of interest were disclosed.

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